Diaphysial Aclasis (Multiple Exotoses) on Guam

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INTRODUCTION

DIAPHYSIAL ACLASIS is a hereditary disease characterized by multiple osteochondromata. The tumors appear to arise between the ages of 4 and 8, are benign and involve chiefly the axial skeleton; the ends of the long bones being the most common site of origin. The tumors grow with the child, and other skeletal abnormalities are often present, particularly bowing and shortening of the long bones. Bone cysts and enchondromata are also frequently observed in these patients. It is estimated that at least 10 per cent of affected persons develop a chondrosarcoma at the site of a tumor during their adult life. Monographs on the disease have been written by Stocks and Barrington (1925), and by Jaffe (1943).

Twenty-one cases of diaphysial aclasis were observed among the Chamorros of Guam (in the Marianas) during a period of 6 months. In this paper, we report our experience with this disease on Guam, and review some of the literature on its genetics and pathogenesis.

PRESENT DATA

A. *Frequency*

The frequency of diaphysial aclasis in Europe and North America apparently is unknown. Stocks and Barrington (1925) compiled 1189 cases from the world literature. Jaffe (1943) reported on 28 patients who had been treated at the Hospital for Joint Diseases in New York. He states that the disease, "... though not exactly common ... is by no means rare." Dr. E. B. D. Neuhauser, in a personal communication, has estimated that at the Children's Medical Center, Boston, approximately one new case per year is uncovered in the out-patient department. The out-patient department has about 90,000 annual visits.

On Guam from October, 1958 to February, 1959, 21 cases were obtained from the families of 6 propositi. All the patients were "Chamorros", a micronesian people who live in the Mariana Islands. On Guam, the principle inhabited island of the Marianas, an accurate census (Report 1959) revealed 32,000 Chamorros of all ages. The exhaustiveness of our own survey, however, is difficult to deter-

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mine. We estimate, on the basis of a survey of school children in two villages, that more than 50 per cent of the cases on Guam were discovered and place the order of the prevalence of the disease at 10^{-3}.

We are, at present, unable to infer that the disease is endemic on Guam. Amyotrophic lateral sclerosis, however, and a syndrome characterized by basal ganglion symptoms and dementia have been shown to be endemic on the Island (Kurland and Mulder 1954; Hirano, Krooth, and Kurland 1961). The etiology of these latter two diseases is not yet clear.

B. *Genetics*

1. *Pedigrees*

Pedigrees of the six propositi are given in Figs. 1 through 4. These families provided a total of 21 ascertained cases. All propositi and other persons shown as affected were x-rayed. Radiologic bone surveys were obtained on adults and adolescents, and a film of the long bones on children.

The pedigrees in Figs. 1 through 3 are consistent with autosomal dominant

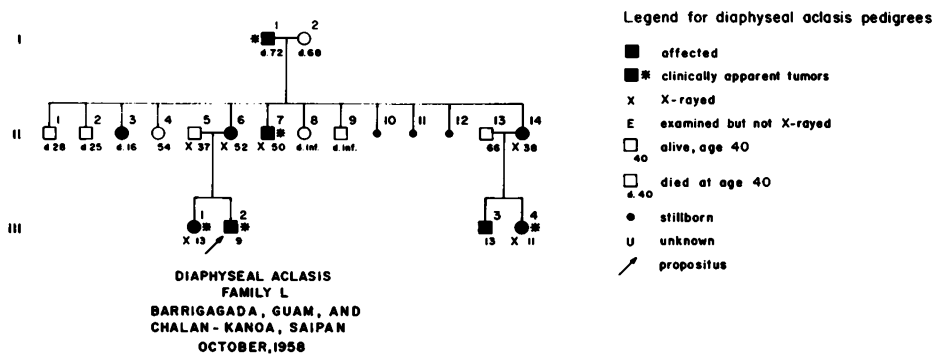

FIG. 1

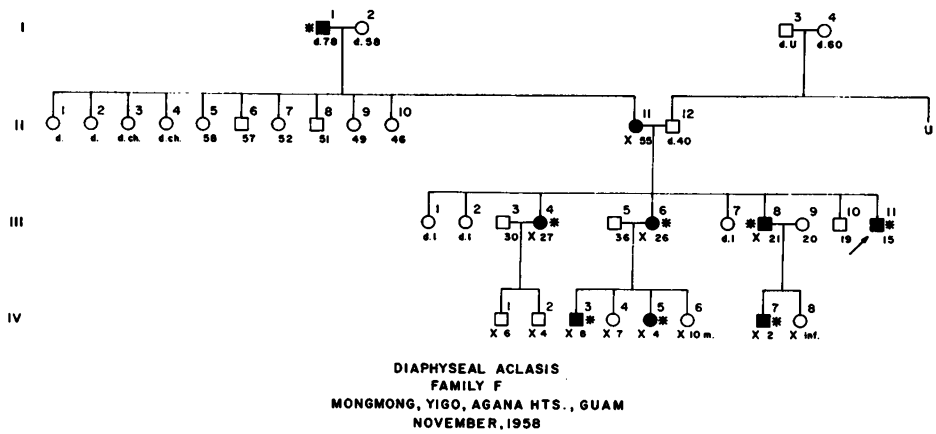

FIG. 2

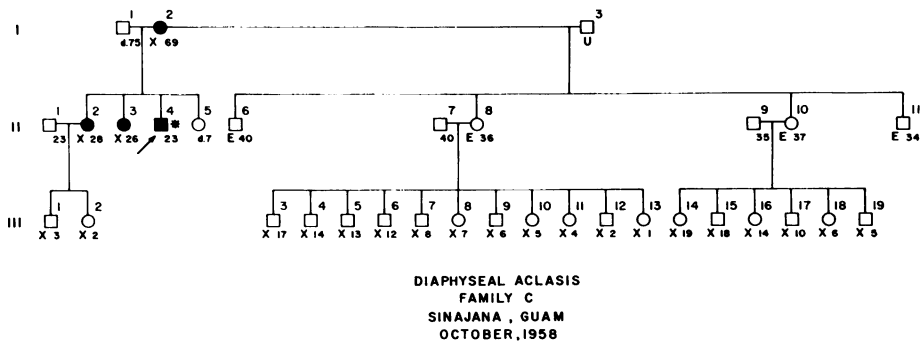

FIG. 3

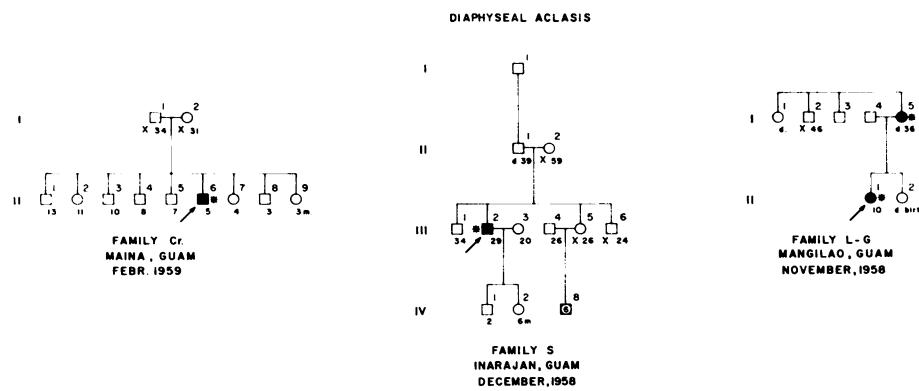

FIG. 4

heredity. The same is true of the "L-G" family in Fig. 4. The proband in the "S" family (Fig. 4) appears to be a sporadic case in the sense that the mother's bone survey was unremarkable, and no history of the father (II-1) being affected was obtained. However, for linguistic and cultural reasons, great reliability cannot be placed on purely amnestic data in this series.

The Cr family (Fig. 4) is considerably more difficult to explain on the hypothesis of simple dominance. Here both parents were examined and x-rayed, and found unaffected. The family was fairly cooperative, spoke and understood English perfectly and were well-educated. There was no *a priori* reason to question the paternity of the propositus, and social data on the family lent no support to such a possibility. Blood was drawn for typing and grouping, and although the specimens were somewhat hemolyzed in transit, data on most of the antigens were obtained. (Typing was carried out at the Blood Bank of the Clinical Center of the National Institutes of Health. We are grateful to Dr. Paul Schmidt in whose laboratory the determinations were done.) The results were:

II-1—O, MN, U^+, P^-, Cc, D, Ee, Kell(−), Fy^a, Jk^a
II-2—O, MN, U^+, P^-, C, D, e, Kell(−), Fy^a
III-5—O, MN, U^+, P^-, C, D, e, Kell(−), Fy^a

These data are therefore consistent with legitimacy. It was unfortunately not possible to obtain x-rays on other members of the family.

2. *Interpretation*

Most of the cases compiled by Stocks and Barrington (1925) were familial. The pedigrees usually showed direct transmission and no consanguinity. Both sexes were affected. Segregation occurred in many of them. It appeared, therefore, that insofar as the disease was genetic, an autosomal dominant gene might be involved. However, males were affected twice as often as females, a fact also noted by Jaffe (1943) in his series. Harris (1948) re-examined Stocks and Barrington's data and observed, among suitably informative families, that when the mother was affected the sex-ratio among affected offspring was 1:1, while when the mother was unaffected the ratio was 2:1. Finally, when the mother was unaffected, but, on the basis of her ascendancy, appeared to be transmitting the disease, the sex-ratio was 3:1.

Harris postulated that disaphysial aclasis was due primarily to an autosomal dominant gene, but that a second, independently segregating autosomal dominant could suppress the disease in the female. Using this hypothesis and the Hardy-Weinberg relations, he was able to predict the frequency of affected males and females from different classes of matings. These predictions were tested against Stocks and Barrington's (1925) data, and good agreement was obtained. It is of incidental interest that Harris estimated the frequency of the hypothetical modifying gene to be about 30 per cent, on the basis of Stocks and Barrington's (1925) data. If the gene does in fact exist, it presumably represents a genetic polymorphism. [Whether it is the Rh negative gene, *r* (c d e), or some other already recognized polymorphic gene, is of course unknown.]

Our own series appears to be consistent with Harris's (1948) suggestion, but is too small to permit us to test his theory further. Certainly the S and Cr families (Fig. 4) might be explained by such a segregating suppressor gene in the family. It is interesting to note that a number of affected adult females had no clinical signs of the disease [e.g. II-14 in family L (Fig. 1) and II-11 in family F (Fig. 2)], but were found unquestionably to be affected on x-ray examination. This was not true of any of the males who were examined. The relatively greater obesity of the adult females may have been a factor, but even on x-ray the discrepancy between the sexes in the size and number of tumors was apparent. The females were not always less severely affected, but from patient to patient seemed more variable with respect to severity than the males. The males in all cases had many large tumors.

The distribution of the patients in this series by sex of affected parent is as follows:

Parent Affected	Males	Females	Total
Mother	5	8	13
Father	2	3	5
Uncertain	2	1	3
Total	9	12	21

Although these data in themselves do not show the effect Harris described, they are small in number and, except for the total sex-ratio, do not differ significantly from the ratios in Harris's (1948) tables. It is of interest that 5 of the 6 propositi were males (Figs. 1 to 4), again indicating that the male is more apt to be conspicuously affected. Perhaps, it is rather rare for the disease to be so completely suppressed in the female that even x-ray studies disclose no involvement. The Cr family is the only example where this appears a likely possibility.

3. *Transmission of specific tumors*

In general Stocks and Barrington (1925) found no correlation between relatives for site of involvement. There were two exceptions, however. A significant correlation was observed between parent and child for involvement at a few uncommon sites. Secondly, in occasional instances when both parent and child were unilaterally affected at the site of some specific bone there was a significant tendency for both to be affected on the same side.

Our data are too sparse for such an analysis, but they show the absence of a striking correlation for site of involvement, or, comparing adults, for size of tumor at a single site. Figure 5 contains x-rays of members of the L family, the member being identified by his pedigree number. Although the x-rays are not technically perfect, they give some idea of the variation within families of severity of involvement at different sites. Note the pelvic films of the two affected adult sisters II-6 and II-14 (Fig. 5).

C. *Clinical features*

1. *Complaint and history*

The chief complaint of most of the patients in our series was cosmetic, the tumors tending to interrupt the normal contours of the extremities. The proposi-

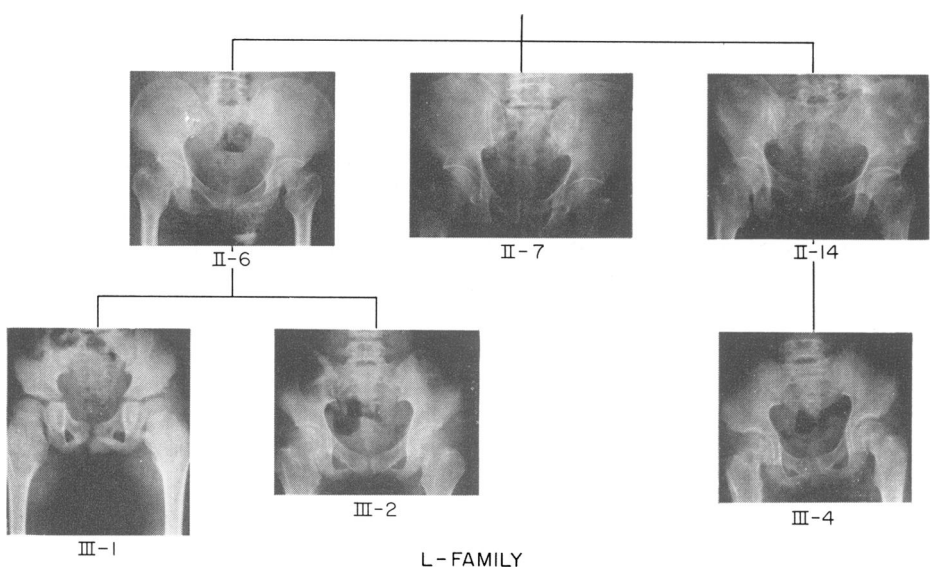

FIG. 5. Pelvic films of the L family.

tus of the S-family sought medical aid when a tumor of the left knee so restricted the joint that the patient was barely able to walk. Patient II-6 in the L family gave a history of dystocia, which is readily understood in view of her pelvic film (Fig. 5). Since the survey was done, one patient not in our present series, was discovered at autopsy to have a metastatic chondrosarcoma.

2. *Physical findings*

In all of the males the tumors were evident on inspection and this was true in half of the females. Tumors were most readily palpable at the wrist, elbow, and clavicle. They could be felt in all males, and six females.

3. *Laboratory examination*

Extensive laboratory determinations were not performed on our patients. Bloods from several patients revealed a normal serum calcium, phosphorous, and alkaline phosphatase. Todd *et al.* (1959 & 1961) have done urinary calcium and phosphorous studies on several patients from the Continental United States and these too were normal. These authors have suggested that the phosphate diuresis in response to injected parathormone may be reduced in patients with diaphysial aclasis. Urine chromatography, kindly performed on specimens from 5 of our patients by Dr. H. Eldon Sutton, then of the University of Michigan, showed no differences when compared with a series of control specimens.

PATHOGENESIS OF DIAPHYSIAL ACLASIS

The classical theories of Keith and Virchow on the pathogenesis of diaphysial aclasis have been critically reviewed by Jaffe (1943). The precise sequence of events which produces the tumors is unknown. Certainly, these osteochondromata differ from most benign tumors in their early age-at-onset. Interestingly, the same is true of solitary osteochondroma (Price, 1958).

Recently Lorincz (1961) has reported that patients with diaphysial aclasis have a mucopolysaccharidurıa. The mucopolysaccharide excreted has been identified as chondroitin sulfuric acid-A. It may therefore eventually be found that patients with this disease have an inherited abnormality either in the synthesis or metabolism of ground substance.

It has also been shown (Ponseti, 1954; Yeager and Hamre, 1957) that young rats fed extracts of the sweet pea (*Lathyrus odoratus*) develop multiple osteochondromata. Such extracts, depending upon the experimental conditions, can induce a variety of connective tissue lesions (Wazonek *et al.*, 1955; Pentschew, 1958; *inter alia*), including dissecting aneurysms, arthritic changes, etc. The effect of the extract can be duplicated by aminoacetonitrile or beta amino proprionitrile (Schilling and Strong, 1954).

The osteochondromata are probably not identical with the human ones. Their histology is somewhat different, for they may contain hematopoetic elements. Moreover, they arise primarily at the sites of muscular attachments to the bone. Hamre and Yeager (1958) have shown that the development of a tumor at a particular site can be prevented by section of the nerve to the muscle inserting at the site.

TABLE 1. SOME GENETIC TUMORS OF MAN

Disease	Genetics
Multiple Neurofibromatosis	Dominant
Xeroderma pigmentosa	Recessive
Adenoma Sebaceum (Epiloia)	Dominant
Diaphysial Aclasis	Dominant
Multiple Polyposis of the Colon	Dominant
Retinoblastoma	Dominant
Lipomatosis	Dominant
Multiple Cutaneous Leiomyomata	Dominant

These findings are of interest primarily because they suggest that a connective tissue poison may induce osteochondromata. In both the human disease and the experimental one, however, it is a little difficult to see how an abnormality in ground substance, assuming this is indeed the primary factor, can lead to a *neoplasm*. In this respect, the nerve section experiments described above are particularly illuminating.

Diaphysial aclasis probably belongs to the general group of inherited abnormalities of mesenchyme, first compiled by McKusick (1956). In virtue of its neoplastic character, however, it may also belong to a second smaller group of diseases. Suppose one makes a list of all the familial human neoplasms one can think of which have the following properties:

1. The disease appears to be due to a single gene.
2. Nearly everyone who has the gene gets the neoplasm.
3. Nearly everyone who has the neoplasm has the gene.

A list of such neoplasms is given in table 1. If one now compares these tumors with neoplastic diseases in general, several features characterizing the former group become evident. First, with the exception of retinoblastoma, which may not satisfy the third requirement listed above, these tumors are benign, at least initially. Secondly the tumors seem to arise from multiple, apparently independent, foci of origin. In the case of retinoblastoma, it has been suggested (Bell, 1922; Best, 1934; Weller, 1941; Franceschetti and Bischler, 1946; Falls and Neel, 1951) that the binocular form is more common among familial than among sporadic cases.

None of these diseases has been shown to involve abnormalities in supporting or connective tissue. They do, however, have a similarity to diaphysial aclasis.

SUMMARY

Twenty-one cases of diaphysial aclasis, noted on the Island of Guam, are reported, and the genetic and clinical features of the disease are discussed.

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